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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

NOGUEROLA, ALEXANDER STEPHAN

ART UNIT	PAPER NUMBER
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1795

MAIL DATE	DELIVERY MODE
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03/09/2009

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/823,503	Applicant(s) BLACKBURN ET AL.	
	Examiner ALEX NOGUEROLA	Art Unit 1795	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 December 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2 and 4-25 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) See Continuation Sheet is/are allowed.
- 6) ☒ Claim(s) See Continuation Sheet is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>12/09/2008</u> | 6) <input type="checkbox"/> Other: _____ |

Continuation of Disposition of Claims: Claims allowed are

8,2/8,4/8,5/8,6/5/8,7/8,9/8,10/8,11,12,13/2/8,14/11/8,15/12/10/8,16/15/12/10/8,17/15/12/10/8,18/15/12/10/8,19/15/12/10/8,20/15/12/10/8,21/8,22/8,23/8,24/8,25/8.

Continuation of Disposition of Claims: Claims rejected are

1,2/1,7/1,9/1,10/1,12/1,13/2/1,14/11/1,15/12/1,17/15/1,18/15/1,19/15/1,20/15/1,21/1,22/1,23/1,24/1,25/1,4/1,5/1,6/5/1.

DETAILED ACTION

Response to Amendment

1. Applicant's amendment of December 05, 2008 does not render the application allowable.

Status of the Rejections pending since the Office action of June 05, 2008

2. All previous rejections are withdrawn.

Claim Rejections - 35 USC § 103

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 1, 2/1, 7/1, 9/1, 10/1, 12/10/1, 13/2/1, 14/11/1, 15/12/1, 17/15/1, 18/15/1, 19/15/1, 20/15/1, 21/1, 22/1, 23/1, 24/1, and 25/1 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/01646 A2 ("Thorp") in view of Ackley US 5,728,532 ("Ackley"), Anderson et al. US 5,922,591 ("Anderson"), Besemer et al. US 5,945,334 ("Besemer"), and Napier "Modification of Electrodes with Dicarboxylate Self-Assembled Monolayers for Attachment and Detection of Nucleic Acids," Langmuir 1997, 13, 6342-6344 ("Napier"). Note that Applicant has replaced "array of detection electrodes" with -- a detection electrode --. So presumably only one electrode is required, although "detection electrodes" is used in the claim.

Addressing claim 1, Thorp discloses a method of detecting a target analyte in a sample comprising:

a) adding said sample to a detection chamber (electrochemical cell – page 46, lines 06-07), comprising a detection electrode (page 46, line 07 and page 16, lines 06-15) and comprising a self assembled monolayer of a capture ligand (page 45, lines 08-16 and Figures 4, 7, and 10– although the term "self-

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assembled" is not used one would understand that the monolayer is self-assembled as defined in Applicant's specification paragraph [0133] because the support is just placed in a solution of only the capture ligand, soaked for one hour, and then dried);

b) allowing the target analyte to bind to the capture ligand to form an assay complex, wherein said assay complex further comprises at least one electron transfer moiety (ETM) (see page 45, lines 29-32 and page 46, lines 06-10. In this example the electron transfer mediator is $\text{Ru}(\text{bpy})^{2+}$); and

c) detecting the presence of said ETM using the detection electrode (see page 46, lines 06-10 and Example 1 at the bottom of page 35).

Also, see claim 40 in Thorp, which claims a similar method as set forth in Applicant's claim 1.

Thorp does not mention providing detection electrodes in the Example 11 embodiment, which relied on above. As noted above Applicant appears to have intended only a single detection electrode. In any event, to provide more than one detection electrode is merely multiplication of parts for multiplication of the desired effect. Providing an array of detection electrodes will allow many different analytes in the sample to be detected simultaneously if each detection electrode has a probe for a

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different analyte. Indeed, to provide a plurality of electrodes is taught by Thorp in a general sense. See page 34, lines 12-21.

Thorp also does not mention mixing the sample when it is contacted with the capture ligand. Anderson and Besemer discloses mixing target sample such that target analyte binds to capture ligand to form an assay complex. See in Anderson col. 02:19-38; col. 12:50-56; and col. 15:04-11 and in Besemer col. 01:61-64 and col. 15:15-44. It would have been obvious to one with ordinary skill in the art at the time of the invention to mix the sample as taught by Anderson and Besemer in the invention of Thorp as modified by Ackley because Thorp as modified by Ackley perform hybridization and as taught by Anderson, "Typically, sample is mixed during hybridization to enhance hybridization of nucleic acids in the sample to nucleic [sic] acid probes on the array," and as taught by Besemer mixing shortens the incubation period of hybridization. See in Anderson col. 15:04-11 and in Besemer col. 15:39-41.

Thorp appears to disclose having the capture ligand as the self-assembled monolayer. Napier discloses Indium Tin Oxide electrodes ("ITO") modified by formation of self-assembled monolayers of 1,12-dodecanedicarboxylate acid further derivatized with DNA. See the abstract. So Napier discloses a detection electrode comprising a self-assembled monolayer and a capture ligand bound to the self-assembled monolayer. It would have been obvious to one with ordinary skill in the art at the time of the invention to have the capture ligand bound to a self-assembled monolayer on the detection electrode as taught by Napier in the invention of Thorp because (1) both

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Thorp and Napier use an ITO electrode, $\text{Ru}(\text{bpy})_3^{2+}$ as ETM, and detect nucleic acids, and (2) Napier discloses

The electrochemistry of $\text{Ru}(\text{bpy})_3^{2+}$ is unaffected by the formation of the monolayer ...; however, the attachment of DNA to the electrode leads to a large catalytic enhancement due to the oxidation of guanine by the oxidized metal complex... This arrangement can be used to detect the hybridization of poly[G] to an electrode modified with poly[dC], providing a new type of DNA hybridization sensor. Importantly, the carboxylate- ITO interface is compatible with the electrochemistry of $\text{Ru}(\text{bpy})_3^{2+}$ at $E_{1/2} = 1.05\text{V}$ (vs Ag/AgCl), ...
See the abstract

Addressing claim 2/1, for the additional limitation of this claim see in Thorp the abstract and page 45, lines 05-07 and the abstract in Napier.

Addressing claim 7/1, for the additional limitation of this claim note a variety of mixing methods, including electrophoretic mixing, was known at the time of the invention. See, for example, col. 15:04-15 in Anderson. Barring a contrary showing, the choice of mixing method from known mixing methods was within the skill of one with ordinary skill in the art at the time of the invention. The choice of mixing method would be based on convenience of incorporating the necessary mixer elements into the detection device and the desired degree of agitation, for example, highly turbulent mixing or mild mixing of reagent in the solution.

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Addressing claim 9/1, as may be inferred from Figure 7 in Thorp the monolayer insulates against one or more of nonspecific binding and nonspecific signaling. One with ordinary skill in the art at the time of the invention that the monolayer is actually denser than shown and will similarly be present on the detection electrode in Napier.

Addressing claim 10/1, for the additional limitation of this claim see Figure 9 in Thorp and Figure 4 in Ackley.

Addressing claims 12/10/1 and 13/2/1, for the additional limitations of these claims see in Thorp the abstract; page 08, line 24 – page 09, line 12; Example 12, which begins on page 46; and Thorp claim 40.

Addressing claims 14/11/1 and 15/12/1, for the additional limitations of these claims note that Napier discloses using $\text{Ru}(\text{bpy})_3^{2+}$ as ETM. Since $\text{Ru}(\text{bpy})_3^{2+}$ is used to detect the DNA in sample introduced to the detection electrode it is also a hybridization indicator. See in Napier **Results and Discussion – DNA Detection**.

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Addressing claims 17/15/1, 18/15/1, 19/15/1, 20/15/1, 21/1, 22/1, 23/1, 24/1, and 25/1, Thorp and Napier discloses that any electrochemical method may used, such as voltammetry and chronoamperometry. See in Thorp page 16, line 28 to page 17, line 07 and the abstract and Figure 1 in Napier. Barring a contrary shown, such as unexpected results, in light of Thorp and Napier capacitance and impedance as obvious variants of the particular example electrochemical methods listed.

5. Claim 4/1 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/01646 A2 ("Thorp") in view of Ackley US 5,728,532 ("Ackley"), Anderson et al. US 5,922,591 ("Anderson"), Besemer et al. US 5,945,334 ("Besemer"), and Napier "Modification of Electrodes with Dicarboxylate Self-Assembled Monolayers for Attachment and Detection of Nucleic Acids," Langmuir 1997, 13, 6342-6344 ("Napier"). as applied to claims 1, 2/1, 7/1, 9/1, 10/1, 12/10/1, 13/2/1, 14/11/1, 15/12/1, 17/15/1, 18/15/1, 19/15/1, 20/15/1, 21/1, 22/1, 23/1, 24/1, and 25/1 above, and further in view of Zanzucchi et al. US 5,585,069 ("Zanzucchi") and Batchelder US 4,390,403 ("Batchelder").

Thorp as modified by Ackley, Anderson, Besemer, and Napier does not mention accomplishing mixing using an AC field or DC pulse, although Anderson does disclose electrophoresis mixing (col. 15:04-19), which suggests mixing using a pulsed DC field (many times reversing, that is pulsing, a DC field). Also, at the time of the invention it was known to use an AC field or non-uniform field to stir reactants in a microfluidic chamber. See in Zanzucchi the abstract and col. 08:20-26 and Batchelder US 4,390,403 ("Batchelder"). Barring a contrary showing, the choice of mixing method from known mixing methods was within the skill of one with ordinary skill in the art at the time of the invention. The choice of mixing method would be based on convenience of incorporating the necessary mixer elements into the detection device and the desired degree of agitation, for example, highly turbulent mixing or mild mixing of reagent in the solution.

6. Claims 5/1 and 6/5/1 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/01646 A2 ("Thorp") in view of Ackley US 5,728,532 ("Ackley"), Anderson et al. US 5,922,591 ("Anderson"), Besemer et al. US 5,945,334 ("Besemer"), and Napier "Modification of Electrodes with Dicarboxylate Self-Assembled Monolayers for Attachment and Detection of Nucleic Acids," Langmuir 1997, 13, 6342-6344 ("Napier"). as applied to claims 1, 2/1, 7/1, 9/1, 10/1, 12/10/1, 13/2/1, 14/11/1, 15/12/1, 17/15/1,

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18/15/1, 19/15/1, 20/15/1, 21/1, 22/1, 23/1, 24/1, and 25/1 above, and further in view of Zanzucchi et al. US 5,585,069 ("Zanzucchi").

Thorp as modified by Ackley, Anderson, Besemer, and Napier does not mention accomplishing mixing through the use of mixing particles, particularly microparticulate matter. However, it was known at the time of the invention to use microparticulate matter for mixing (Zanzucchi -col. 08:20-26. The mixing particles are implicitly microparticulate since the wells have micron sized dimensions – col. 07:11-14). Barring a contrary showing, the choice of mixing method from known mixing methods was within the skill of one with ordinary skill in the art at the time of the invention. The choice of mixing method would be based on convenience of incorporating the necessary mixer elements into the detection device and the desired degree of agitation, for example, highly turbulent mixing or mild mixing of reagent in the solution.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 1 recites the limitation "said detection electrodes" in 10. There is insufficient antecedent basis for this limitation in the claim.

Allowable Subject Matter

9. Claims 8, 2/8, 4/8, 5/8, 6/5/8, 7/8, 9/8, 10/8, 11, 12, 13/2/8, 14/11/8, 15/12/10/8, 16/15/12/10/8, 17/15/12/10/8, 18/15/12/10/8, 19/15/12/10/8, 20/15/12/10/8, 21/8, 22/8, 23/8, 24/8, and 25/8 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

10. The following is a statement of reasons for the indication of allowable subject matter:

a) Claim 8: the combination of limitations requires each of the detection electrodes to be “sunken” or “recessed” with respect to the chamber, such that the flow of the sample past each of the detection electrodes causes the mixing. In Thorp and Ackley the detection electrodes are instead “raised” with respect to the chamber. See Figures 9 and 10 in Thorp and Figures 1 and 4 in Ackley.

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b) Claims 2/8, 4/8, 5/8, 6/5/8, 7/8, 9/8, 10/8, 11/8, 12/10/8, 13/2/8, 14/11/8, 15/12/10/8, 16/15/12/10/8, 17/15/12/10/8, 18/15/12/10/8, 19/15/12/10/8, 20/15/12/10/8, 21/8, 22/8, 23/8, 24/8, and 25/8 depend from allowable claim 8.

c) Claims 11 and 12: each combination of limitations requires the capture ligand to be bound to the self-assembled monolayer using biotin and streptavidin. In Thorp as modified by Ackely, Anderson, Besemer, and Napier the monolayer is derivatized with the capture ligand (DNA) "via reaction of the pendant carboxylate with endogenous amines of the nucleobases following activation with water-soluble carbodiimide." See the Thorp abstract.

Information Disclosure Statement

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11. Applicants are requested to provide copies of the following references listed on the Information Disclosure Statement received on December 09, 2008 – B8, B10, B11, B19, B24, B32-B36, B41, B42, B44-B50, C13, C15, C18, C23, C39, C40, C44, C48, C54, C55, C60, C61, C68, C69, C73, C90, C91, C98, C104-C106, C117, C118, C121, C122, C136, C139, C141, C143, C145-C148, C153, C156, C159, C164, and C167.

Final Rejection

12. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

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the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALEX NOGUEROLA whose telephone number is (571) 272-1343. The examiner can normally be reached on M-F 8:30 - 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, NAM NGUYEN can be reached on (571) 272-1342. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Alex Noguera/
Primary Examiner, Art Unit 1795
March 6, 2009